Date of decision: March 3, 2026

RISK ASSESSMENT SUMMARY

Type VII Veterinary Master File 006-645
Type VII Veterinary Master File 006-697

Heritable insertion of the Celtic allele in cattle (*Bos taurus*) [g.(NC_037328.1) dup(2429109-2429320) + del(2429327-2429336)]

The IGA is intended to introduce the Celtic allele into an intergenic region of bovine autosomal chromosome 1 to generate the polled phenotype in cattle that are intended to be used as sources of food.

Developed by:

Acceligen

Executive Summary

Acceligen developed an intentional genomic alteration (IGA) in cattle using genome editing to insert the Celtic polled (Pc) allele in an intergenic region (between *IFNAR2* and *OLIG1*) and generate a polled (hornless) phenotype. The IGA is equivalent to genomic sequences that exist in conventional cattle with a history of safe use in animal agriculture and food production. Animals with the IGA are known as Celtic polled cattle (Pc-Polled cattle). The IGA is heritable and can be passed on to offspring, allowing the trait to be propagated into horned cattle through breeding and conventional means. The IGA was generated in four founder animals, two Black Wagyu bulls and two Line 1 Hereford bulls. For these founder Pc-Polled cattle, FDA evaluated data and information on molecular characterization, animal health, food safety, and environmental considerations. FDA will review similar data and information for the generation of any additional founder animals prior to marketing.

Molecular Characterization

This IGA was generated using CRISPR-Cas12a genome editing. FDA reviewed sequencing data to confirm the IGA and screening methods for potential off-target genomic alterations in the founder Pc-Polled animals. The Pc-Polled animals are equivalent to naturally occurring variants found in certain cattle breeds originating in Europe.

Phenotypic Characterization / Animal Health

FDA reviewed information to show that Pc-Polled cattle have the intended polled (hornless) phenotype as seen in naturally occurring polled breeds. FDA reviewed data to demonstrate that Pc-Polled cattle are comparable to conventional cattle of the same breed with respect to growth, health, and development.

Food Safety

FDA did not identify any human and animal food safety concerns associated with the IGA in cattle. FDA determined that food products derived from Pc-Polled cattle are as safe as food products derived from conventionally raised cattle with the polled phenotype that are commonly consumed by the public.

Environmental Risk

FDA did not identify any environmental hazards with regard to the IGA and concluded that the phenotype produced by the IGA is a well-established trait in several breeds of conventionally raised domestic cattle in the United States (U.S.). In addition, the likelihood of escape and establishment of cattle with the IGA in the U.S. environment is low due to the ability to rapidly recover escaped animals and the lack of feral cattle populations in the U.S. Therefore, these Pc-Polled cattle can be held at any facility in the U.S. with no required conditions of containment or carcass and waste disposal beyond those used for conventional domestic cattle and the risk to the environment resulting from the IGA contained in Pc-Polled cattle is low.

Conclusions

Based on the data and information reviewed, FDA concluded that Pc-Polled cattle are equivalent to conventional cattle with naturally occurring Celtic polled variants and that the risks are appropriately mitigated. The agency does not object to the marketing of these Pc-Polled cattle or their products.

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I. GENERAL INFORMATION

A. File numbers

VMF 006-645
VMF 006-697

B. Developer

Acceligen

C. Product established name

Heritable insertion of the Celtic allele in cattle (*Bos taurus*) [g.(NC_037328.1) dup(2429109-2429320) + del(2429327-2429336)]

D. Product category

Intentional genomic alteration (IGA) in animals

E. Species

Cattle (*Bos taurus*)

F. Claim

The IGA is intended to introduce the Celtic allele into an intergenic region of bovine autosomal chromosome 1 to generate the polled phenotype in cattle that are intended to be used as sources of food.

II. INTRODUCTION

FDA assessed the potential hazards and likelihood of harm associated with the use of the IGA. The IGA is the insertion of the Celtic polled (Pc) allele to generate the polled (hornless) phenotype in cattle (animals with this IGA are referred to as Pc-Polled cattle). The subjects of this risk review were four founder Pc-Polled bulls (two Black Wagyu and two Line 1 Hereford). FDA evaluated data and information to show that Pc-Polled cattle are equivalent to comparator animals with the naturally occurring Celtic allele that have a history of safe use in animal agriculture. FDA evaluated descriptions of the methodology used to generate the IGA, characterization of the genomic sequence and potential unintended alterations resulting from the introduction of the IGA, animal health and safety data, food safety information, and information on the risk of impacts on the environment.

To support a history of safe use of the naturally occurring Celtic allele in cattle used for food, FDA evaluated literature supporting that the naturally occurring Celtic allele was first reliably identified in animals dating from 4000 B.C.E. and was well-established in farmed cattle used for agricultural purposes by the late 1700s. The naturally occurring Celtic allele originated in Northern Europe; although the genotype of those polled cattle is not known, a recent genotyping study of nearly 60 breeds of cattle suggested that the Celtic allele evolved in Nordic breeds at least 1000 years ago.[1] In a study of polled European breeds, the naturally

1 Allais-Bonnet A, et al. Novel insights into the bovine polled phenotype and horn ontogenesis in Bovidae. PLoS One. 2013 May 22;8(5):e63512. doi: 10.1371/journal.pone.0063512. PMID: 23717440.

occurring Celtic allele was found in a majority of breeds tested, including breeds used for human food since at least the 1800s (e.g., Aberdeen Angus, Hereford, Charolais).

FDA's decision is based on our evaluation of the data and information described here and is limited to the individual Pc-Polled cattle that were reviewed by FDA and their offspring. In the future, FDA may review similar data and information from additional founder Pc-Polled animals, including founder animals in additional breeds. FDA will review similar data and information for the generation of any additional founder animals prior to marketing.

III. MOLECULAR CHARACTERIZATION

The Pc allele is a single complex insertion/deletion wherein a 212-base-pair duplication replaces a 10-base pair sequence.[2] It is located in an intergenic region on bovine autosomal chromosome 1 (between *IFNAR2* and *OLIG1*). Based on FDA's review, the IGA does not disrupt known coding sequences, splice sites, intronic regions, or regulatory regions. There is no known transcript or protein associated with the Pc allele.

A. Mechanism of generating the IGA and founder animals

The IGA was generated in the founder Pc-Polled animals using standard molecular biology techniques. The IGA was introduced into bovine embryonic stem cell lines via CRISPR. Both Black Wagyu founder animals were derived from an edited cell line, resulting in cloned animals. The Line 1 Hereford founder animals were derived from two distinct cell lines. The genome editing steps were performed using adequate procedural controls and incorporating sufficient tests to ensure quality during production.

B. Whole genome sequencing (WGS)

WGS data for the four Pc-Polled founder animals and their respective unedited (wildtype) cell lines were assessed for quality, to confirm the IGA, and to identify short and large genomic alterations present in founder animal(s) but not the respective unedited (wildtype) cell lines. Identified alterations were assessed for proximity to off-target sites (from *in silico* predictions) and genes (from annotation databases including Ensembl, NCBI, and UniProt). FDA determined the data to be of sufficient quality for identification of intended and unintended alterations in the founder animals. The WGS data confirmed the homozygous introduction of the IGA in all four founder animals.

Both Black Wagyu founder animals (derived from the same edited cell line) had an expansion of a copy-neutral loss of heterozygosity (CN-LOH) region in their unedited cell line approximately 1 megabase downstream of the target site. CN-LOH is a genomic change in which one copy of a chromosomal region is replaced by a duplicate of the other copy of the chromosome, without any net gain or loss of genomic sequence, and it does not result in the introduction of any novel genomic sequence. Given the far distance of the CN-LOH from the target site and the occurrence of CN-LOH in naturally bred animals, it is unclear if the CN-LOH event in the founder animals is attributable to the introduction of the IGA or occurred spontaneously, independent of the introduction of the IGA. Based on the absence of a net gain or loss of genomic sequences, there were no identified risks resulting from the presence of the CN-LOH event.

2 Aldersey JE, et al. Understanding the effects of the bovine POLLED variants. Anim Genet. 2020 Mar;51(2):166-176. doi: 10.1111/age.12915. Epub 2020 Jan 30. PMID: 31999853.

Both Line 1 Hereford founder animals (derived from different edited cell lines) had a tandem duplication that was unique to that founder animal and not present in their respective unedited cell line. The tandem duplications were ~50 to 650 kilobases from a predicted cut site (allowing for five mismatches and two bulges) and thus it is unclear if they are attributable to the introduction of the IGA or occurred spontaneously, independent of the introduction of the IGA. Based on currently available genome annotation data, there were no identified risks resulting from the presence of either tandem duplication.

Conclusions: Based on the review of this data and information, FDA concluded that the IGA as well as identified unintended alterations do not pose a safety concern and do not contain any sequences that may pose risk to humans, animals, and the environment. Based on the review of these data and information, FDA concluded that Pc-Polled cattle have a genotype equivalent to the naturally occurring Celtic allele found in conventionally raised cattle used in animal agriculture food production.

IV. PHENOTYPIC CHARACTERIZATION / ANIMAL HEALTH

A. Intended phenotype

The IGA is intended to produce a polled phenotype (i.e., lack of horns), which can be observed visually. FDA confirmed that the four Pc-Polled founder animals, two Black Wagyu bulls and two Line 1 Hereford bulls, had the expected polled phenotype. These founder animals are homozygous for the Celtic allele. Because this trait is autosomal dominant, heterozygous animals will exhibit the intended phenotype; however, when heterozygous animals are bred to each other, they may produce offspring that do not carry the trait. Published literature[3,4] has documented that heterozygous animals may exhibit the scurred phenotype.

B. Animal health

FDA reviewed information on the health and growth of the four founder Pc-Polled bulls. For the two Pc-Polled Black Wagyu bulls, FDA evaluated veterinary and herdsman health information for up to approximately two years of age (two years and one month and two years and 4 months). One Black Wagyu calf had an umbilical remnant infection that resolved with antibiotic treatment in the first 30 days of age. Umbilical remnant infections are common in conventional calves. For the two Pc-Polled Line 1 Hereford bulls, FDA evaluated veterinary and herdsman health information for up to approximately 11 months of age (11 months and 7 days and 10 months and 24 days). At four and a half months of age, one Line 1 Hereford calf had lameness and distal limb swelling consistent with physitis that resolved with antibiotic treatment and time over two months. Physitis is a common developmental orthopedic disease in beef cattle especially rapidly growing bull calves of this age. The health and growth of these Pc-Polled cattle was consistent with that of conventional animals (i.e., cattle without the IGA) of the same breed. The health information, including the noted health abnormalities, was consistent with conventional calves of the same breed.

3 Ketel C and Asai-Coakwell M. Heterozygosity of the Celtic polled locus in Canadian scurred beef cattle. Canadian Journal of Animal Science. 2020 100(3): 479-484. https://doi.org/10.1139/cjas-2019-0095

4 Tetens J, et al. Association mapping of the scurs locus in polled Simmental cattle--evidence for genetic heterogeneity. Anim Genet. 2015 Apr;46(2):224-5. doi: 10.1111/age.12237. Epub 2015 Jan 23. PMID: 25645725.

Conclusions: Based on the phenotypic data, animal health data and the literature reviewed, FDA concluded that these Pc-Polled cattle exhibit the expected phenotype as seen in conventionally bred animals with the naturally occurring Celtic allele. Coupled with the history of no known safety risks to conventionally raised cattle with the naturally occurring Celtic allele, FDA concluded that the IGA presents a low risk to animal safety.

V. FOOD SAFETY

FDA conducted a safety assessment to determine if the food derived from Pc-Polled cattle is safe for human and animal consumption. Cattle with the naturally occurring Celtic allele have been safely consumed and are already present in the U.S. food supply. The IGA does not produce novel proteins or allergens and does not alter metabolic pathways that could generate a hazard. Polled cattle carrying the Celtic allele through traditional crossbreeding have existed in the food supply for years, with genome-edited cattle differing only in the method of introducing the trait. Pc-Polled cattle are phenotypically and genotypically no different from naturally occurring polled cattle, with no anticipated differences in carcass composition, meat quality, or nutritional content compared to horned cattle.

Conclusions: FDA did not identify any hazards from the IGA with respect to the safety of food derived from the polled founder bulls and their progeny. FDA concluded that the safety of food products derived from these Pc-Polled cattle is no different from that of food products derived from commercial cattle without the IGA, including those with naturally occurring polled phenotypes. This assessment supports the use of Pc-Polled cattle as a safe source of edible products for human consumption.

VI. ENVIRONMENTAL RISK

FDA evaluated the potential risk to the environment from the marketing of the IGA in cattle and associated products derived from them. The information provided by the developer is adequate to demonstrate that the IGA and alteration process do not pose a hazard to the environment and produce a phenotype that exists in other domesticated cattle present in the United States (U.S.). FDA's evaluation assumed that the Pc-Polled cattle will not be held under strict containment and may be housed on any farm in the U.S. In general, cattle are considered low risk for escape and establishment in the natural environment, as they are generally expected to be recovered quickly if escape occurs and there are very few feral bovine populations in the U.S. with which Pc-Polled cattle could breed. In addition, the polled phenotype can be visually confirmed, and typical cattle management practices in the U.S. include use of ear tags for identification. Finally, no environmental hazards were identified with the IGA that would require that manure or carcasses be handled any differently from typical farm practices.

Conclusions: FDA concluded based on the available information, the development and marketing of the IGA contained in Pc-Polled cattle, their derivatives, and their progeny pose a low risk to the environment.

VII. AGENCY CONCLUSIONS

The data and information demonstrate that the IGA in Pc-Polled cattle is equivalent to genomic sequences that are found in animals of the same species with a history of safe use in animal agriculture and food production. We find that we understand the product's risks for the specified intended use, any identified risks, including their potential severity and likelihood of occurring, are appropriately mitigated, and we have no further questions for which we would need to see additional data. Although the IGA in Pc-Polled cattle is not

approved, conditionally approved, or index listed,[5] because FDA has determined the risks associated with the IGA are appropriately mitigated, at this time the agency does not intend to object to marketing the IGA in Pc-Polled cattle or associated products derived from them (i.e., offspring, semen, or embryos) or introducing food derived from Pc-Polled cattle into the human or animal food supply. This decision is limited to the marketed products (e.g., live animals, semen, embryos, meat) derived from the Pc-Polled cattle for which FDA has reviewed data and their progeny.

5 See sections 512, 571, and 572 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. §§ 360b, 360ccc, and 360ccc-1].